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TISSUE CHANGES.

BY

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OF BALTIMORE.

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ON THE RELATIONS BETWEEN ARTERIAL DISEASE AND TISSUE CHANGES.

By WILLIAM T. COUNCILMAN, M.D.,
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I HAVE thought it would be best in the consideration of a subject which embraces so much, to confine my remarks to a study of diffuse arterio-sclerosis, because, not only on account of the importance of the disease, but on account of the extent of the lesions both in the vessels and tissues, it best serves to illustrate the relation of these changes to each other.

It would not be within the scope of this article to attempt to give anything but a very brief reference to the most important publications which have appeared on the subject. When we leave out of consideration the earlier articles on diseases of the arteries, which relate almost exclusively to the histological details of the changes, the first article in which, along with arterial disease and dependent on this, various lesions of the tissues are recognized, is that of Gull and Sutton, published in 1871. They describe, under the name of arterio-capillary fibrosis, a general disease characterized by the formation of a peculiar hyaline fibroid substance around and in the walls of small arteries and capillaries. This hyaline substance is sometimes homogeneous, sometimes slightly striated. They first describe the changes which take place in the kidneys. In the affected vessels outside of the muscular coat the hyaline fibroid substance forms a layer thicker than this. The vessels are rendered thicker, more tortuous, and the lumen is often encroached upon or completely obliterated. The tubules of the kidney are atrophied, dilated into cysts, and the epithelium finely granular, shrunken, and wasted. The hyaline fibroid tissue appears to commence in the outer coats of the arteries and in the capillary walls, and from these it extends around the glomeruli

and the tubules. By the contraction of this substance the vessels are compressed, the blood-supply in different parts is diminished, and atrophic changes result, or, at the same time with the changes in the vessels and interstitial tissue, changes may be taking place in the cells. The result of the pathological processes in the kidney is the granular contracted kidney. Changes identical to those in the vessels of the kidney are found everywhere, and are especially well marked in the pia mater. In all these tissues the change begins in the adventitia of the vessels and extends into the surrounding tissues and often toward the lumen.

Gull and Sutton differ in their conception of the arterial change from Johnson, who claimed that only the muscular coat of the arteries was thickened. They recognize the fact that in the larger arteries the intima is often thickened and that the nuclei of the muscular layers do not stain distinctly. While the changes in the kidneys are the most marked and the symptoms during life are most indicative of renal disease, they do not constitute an indispensable part of the process. When the larger arteries are affected the intima is also much thickened, and the nuclei of the muscular fibres do not stain well. The heart is always hypertrophied, and this is due to the vascular changes. The disease commonly begins in the kidneys, but in some cases they are but little, if at all, affected, while the change may be far advanced in other organs. It will be seen that the great value of this article of Gull and Sutton's is, that they claim the whole as a general disease of the vascular system. There is no doubt that their general conception of the pathological histology of the process is wrong.

Next in importance to this work of Gull and Sutton is that of Thoma, who, in a series of articles in Virchow's *Archiv*, has considered the whole subject of arterial changes and the laws under which they take place. It is difficult to find in the whole domain of pathology any work more thorough and painstaking than this of Thoma's; in fact, the extent of it and minutiæ with which every idea is followed out, and the further difficulty which the reader has in following the ideas of Thoma, will always stand in the way of its becoming popular reading. He starts out with the study of the fœtal aorta and the changes which take place in this after birth as the result of the occlusion of the ductus Botalli and the umbilical arteries. In the last

weeks of fœtal life the umbilical arteries are the most important branches of the aorta, and, in consequence of their closure, there must be a considerable variation between the width of the aorta and its various branches, although this is partly compensated for by the widening of the arteries of the stomach, kidneys, and intestines. This disproportion between the aorta and its branches extends from the umbilical arteries up to the ductus Botalli, and he finds that, strictly limited to this part of the aorta, there is a formation of connective tissue in the intima by which the width of the vessel is reduced to a normal relation.

This formation of connective tissue he thinks is due to a slowing of the circulation in the abnormally wide vessels, and he asserts, as a general law, that when there is an abnormal relation between the size of an artery and the territory which it supplies, a compensating endarteritis is set up which brings back the relations to the normal standard. He explains in the same way, the endarteritis which takes place in the arteries of an amputated extremity, or in arteries everywhere as soon as there is a disproportion between their calibre and the amount of tissue they supply.

In his studies on arterio-sclerosis he makes two forms. One of these he calls primary arterio-sclerosis, and here the process is set up by local changes in the artery affected which lead to a dilatation, and in consequence of this and in accordance with the law, an increased formation of connective tissue in the intima tends to reduce the artery to normal relations. The other form is the secondary arterio-sclerosis, and this is due to changes in the arterial wall caused by increased resistance to the flow of blood in distant organs. In every case it is the slowing of blood-current and the dilatation which brings about the connective-tissue formation. It is this second variety which corresponds to the disease described by Gull and Sutton. In all these cases the primary change in the vessels is a degeneration of the media. In the aorta it is this degeneration which allows the vessel to dilate, and in consequence of this dilatation the sensitive nerve-endings in the vessel's walls, the Pacinian corpuscles, are irritated. This leads to a dilatation of the vasa vasorum, and an excitation of the trophic nerves, causing a new formation of connective tissue. This explanation of the process must be considered extremely hypothetical, and one for which there is no analogy in pathology. It will be seen from

this that Thoma supposes the changes in the aorta in the second variety to be only the result of changes in the arterioles of distant organs. The nodular form of arterio-sclerosis is due to circumscribed dilatations of the arteries and a new formation of connective tissue which exactly fills out the dilated area. When such arteries are examined after having been injected with paraffine under a pressure of 16 cm. of mercury, the raised plaques which are so prominent in the uninjected vessels have entirely disappeared, leaving a smooth intima — the primary changes here having been a local dilatation and a local increase of connective tissue which compensates for the dilatation.

Our study of arterio-sclerosis, in which we have been associated with Dr. W. T. Howard, is based on the examination of forty-one cases which have been autopsied at the Johns Hopkins Hospital since its opening, two and a half years ago. These can be divided into three classes. In such a division we are beset with the difficulties which always accompany a classification of pathological conditions based on anatomical lesions alone. While we undoubtedly find typical cases of each class, many cases are seen which cannot be brought under hard and fast lines of division, but represent more or less mixed forms, and must be placed in the class to which the more prominent changes belong. The first of these divisions, the nodular form of arterio-sclerosis, has little interest for us. In this the changes are limited to the aorta and large arteries, and we find along the course of the vessel, which is otherwise smooth and of normal calibre, elevated plaques, sometimes translucent and cartilaginous in appearance, sometimes calcified or softened. The description of Thoma applies perfectly to these. The growth is entirely within the intima, and the media at the point affected is thin and degenerated.

The second form is the senile endarteritis. In the most typical cases of this the aorta and all the larger arteries are converted into almost rigid calcareous tubes. The inner surface is rough, and there are frequently fissures and losses of substance to which thrombi may adhere. The arteries are not only irregularly dilated, but they are elongated as well, this being seen in the formation of curves in the course of the artery where none normally exist, and in the marked accentuation of normal curves. Notwithstanding the extent of the calcareous infiltration, the walls of the arteries are thinner than

normal. The heart is small, often showing the condition of brown atrophy, and there are similar atrophic changes in the other organs, best marked in the liver and kidneys. The kidneys are smaller than normal, their color little, if any, changed, the surface slightly granular with frequently depressions of greater depth in places where a more extensive loss of substance has taken place. On section of the kidney it is seen that both cortex and pyramids are concerned in the atrophy, the cortex suffering most. On the section the cut ends of the smaller renal arteries project above the surface and are frequently calcareous. On microscopic examination there is both an increase in the connective tissue and atrophy and loss in the parenchyma. The tubules are shrunken or in places converted into cysts, the epithelium smaller and more granular, the glomeruli are in general small, and many of them show all stages of atrophy. When fresh sections of the organ are examined, there is always some fatty degeneration of the epithelium, though often slight in amount. The connective tissue is dense and contains relatively few granulation-cells.

The changes in the liver are very analogous to those in the kidney. There is some atrophy, the organ not weighing more than 1000–1200 grammes, the surface is smooth or slightly wrinkled, and the consistency is increased. On microscopic examination the cells are small, frequently fatty, the capillaries are wider than normal, and there is some increase in the connective tissue. The arteries show lesions very similar to those in the other tissues. There is marked atrophy of all the coats, particularly of the media. The muscular fibres of this become necrotic, hyaline, and finally, by the deposit of calcareous matter in the necrotic tissue, the whole artery is frequently converted into a calcareous tube. The process is strictly one of atrophy and degeneration, and the arteries share in the fate of the tissues generally. In fourteen cases of senile endarteritis, there was entire absence of heart hypertrophy in seven. Of the others, in all of which the heart hypertrophy was of very minor degree, two had diseased aortic valves, and in the other five, the senile changes in the arteries were complicated with other changes which we are about to describe.

The most important class of cases are those belonging to the diffuse arterio-sclerosis, in which the lesions are widely distributed, embracing all the arteries of the body. We are not able to make the sharp distinction here which Thoma does, dividing them into two classes, in

one of which the lesions are local in the vessels and due to local changes, while in the other the lesions in the great vessels are secondary to changes in the small. Contrary to the senile endarteritis, the subjects of this are generally men in the prime of life. In 27 cases of this disease, the youngest, a negro, gave his age as twenty-three; the oldest was sixty. Most of the cases ranged between forty and fifty-five; 14 were white and 13 colored. We find in this disease a very typical pathological picture. Most of the subjects who came to autopsy were strongly-built, well-nourished, muscular individuals. As a rule, there was no œdema either of the face or lower extremities. When œdema was present it had come on in the last few days or weeks of life. Heart hypertrophy is always present and may reach an extreme degree. In two cases in which there were no valvular lesions whatever, the heart in one weighed 850 grammes, and in the other 820. The average weight was over 400. The myocardium is firm and dark. Close examination often shows some degree of fibrous myocarditis, this depending on the degree of involvement of the coronary arteries in the general trouble. The heart hypertrophy may be confined to the left ventricle, but in the most marked cases it is always associated with so much dilatation that the right ventricle also becomes hypertrophied. The dilatation may be so excessive as to affect the integrity of all the valves. Anatomical lesions of the valves are usually absent. There may be some extension of the aortic disease to the aortic valves or the aortic segment of the mitral valve, but the thickening so produced is not generally sufficient to interfere with the functions of the valve. The supposed inflammatory changes in the myocardium described by Buhl and referred to by Thoma, are not found. The most marked changes are found in the aorta and the large arteries given off from this. The large arteries are more or less dilated, the dilatation in some cases starting in the aortic orifice and extending throughout the aorta and large arteries. This dilatation is seldom homogeneous throughout, but in addition to the general dilatation there may be here and there more local dilatations. Some of the measurements of the arteries will show how extensive this dilatation may be. In two well-marked cases the measurements are as follows, the circumference of the vessels being taken in centimetres:

	Case 1.	Case 2.
Just above aortic valves . . .	8	8
In transverse arch	8½	14
In middle of thoracic . . .	7½	9
At diaphragm	6	7
At renals	5	6½
At bifurcation	4½	4

The branches of the arch are sometimes relatively more dilated than the aorta. There is elongation of the vessels as well. The aorta makes lateral curves and the normal curves of other arteries are greatly accentuated. In addition to the dilatation there is a general diffuse thickening of the arteries which is often relatively greater in arteries the size of the radial than in the large. In the large arteries the intima is roughened by projecting elevations which are frequently distinguished by differences in color and consistency. They may be of a pearly, transparent color and very hard, in both color and consistency similar to cartilage. They may be of an opaque, whitish-yellow color, and the centre soft and pultaceous. On incising such places a soft, white, mortar-like mass escapes. We may find irregular, ragged excavations, often covered with fibrin, showing that the softening has extended through the intima of vessel during life. Similar areas of softening and degeneration may be found in the diffusely thickened intima. There may be more or less calcification which is usually confined to the projecting elevations, but this never reaches the same extent here, as in the senile form. There are frequently longitudinal folds and puckering of the intima as though due to the contraction of the vessel after death.

To the naked eye the kidneys sometimes show the most marked lesions, at others the changes are so little apparent that they could easily be passed over. The color of the kidneys varies considerably; generally they are hyperæmic, the extent of this depending upon the greater or less degree of chronic passive congestion which is present. They may not be diminished, or even slightly increased in size; the capsule may strip off easily or be more or less adherent and small portions of the cortex may be removed with it. The surface is usually more or less granular and there are frequently deep depressions showing greater and more localized atrophy. Finally, the appearances may be those of the granular contracted kidney. On section the cortex is generally slightly reduced in thickness and the normal markings

somewhat obscure. The arteries are prominent and project above the cut surface. Even with the naked eye it can be seen that their walls are thicker than normal. The most marked feature of the kidneys is an increased consistency. It is more resistant both to the knife and to attempts to break and tear its tissue.

The liver, to the naked eye, shows little change. It may be somewhat reduced in volume, but generally its weight and dimensions are normal. The capsule is smooth, and the most evident changes are those connected with chronic passive congestion when this is present. It must be remarked that even when a considerable degree of chronic passive congestion is present the changes produced by this in the liver are not so marked as in an uncomplicated heart case. As in the kidney, the most striking change in the liver is the increased consistency. It will be found very difficult to tear or even to thrust the finger into the cut surface, and an increased resistance is given to the knife. The lungs are little, if at all, affected, save by the chronic passive congestion, and the pulmonary artery is nearly always entirely free from disease. There are no noteworthy changes in the other organs save an increased toughness. In several of the cases there was more or less extensive hydrothorax, and in a little less than one-half there was some œdema of the lower extremities. In three of the cases there was general anasarca. Death resulted either from some intercurrent disease or from the arterial lesions alone, and in many cases was sudden. In some of these cases of sudden death, extensive disease of the coronary arteries was found, in others it could not be attributed to this.

The histological examination of the tissues was in most cases confined to the diseased arteries and the liver and kidney. The last two organs were chosen both on account of the importance of the lesions in them, and also from the fact that their tissue offers especial advantages for the study of the small arteries and capillaries. I will spare the Association all the details of the histological changes in the liver and kidney. Briefly, they consist in the kidney, of various degenerative changes in the epithelium, of an increase in the connective tissue, and of widespread lesions in the arteries especially affecting those of very small calibre. The epithelial degeneration consists of simple atrophy of the cells and of granular, fatty, and hyaline degeneration, which is in some cases more focal, in others more diffuse in character.

The same with the increase in connective tissue. This is found both in well-defined streaks running down from the cortex, and in a diffuse thickening of the inter-tubular tissue everywhere. It is, of course, most marked in the regions which correspond to the greatest atrophy of the cortex, shown by the deep depressions on the surface. In these places only remnants of the epithelial structures of the organ are found.

In this connective tissue, tubules in every stage of atrophy can be seen, some entirely collapsed, others irregular in shape, containing but a few degenerated cells, others, again, dilated into small cysts; from these larger bands of connective tissue smaller masses are given off. There is also some diffuse connective-tissue increase. The cells in this newly formed tissue vary considerably in number; in some cases it is dense and contains very few cells, in others it contains numbers of round granulation-cells. There is always a marked change in the arteries, which is always more marked in the smaller ones. The most prominent change is a thickening of the wall, which is due to the formation of a homogeneous hyaline tissue within the muscular coat. This tissue usually contains but few cells, is faintly striated, and stains a light brown with the osmic acid used in the hardening solution. In many of the smallest vessels nothing can be seen of the elastic lamina, in others only fragments of it can be made out, in others it is preserved. The lumen of these most affected arteries is seldom perfectly round, but the newly formed tissue makes irregular projections into the lumen, deforming it in various ways. The muscular fibres of the media show the most marked atrophic changes. Fatty degeneration of the cells can be made out both in the fresh sections and after hardening in Fleming. The nuclei are often very thin and atrophic-looking; vacuoles are sometimes seen in them. In some arteries the nuclei have almost entirely disappeared and the media is changed into a homogeneous tissue very similar to that in the thickened intima. On longitudinal sections of the arteries these changes in the intima were sometimes very apparent. In places where the muscular coat was at first sight but little, if at all, affected, a close examination showed it to have a reticular appearance, a dark-brownish substance forming the reticulum, leaving round spaces between, which correspond to the muscular fibres and in which the muscle nuclei are frequently seen. The tissue between the muscle-cells passes directly into

that of the thickened intima. In the larger renal arteries there is always some degeneration of the media, but it is not so well marked as in the very small.

The glomeruli are variously altered. Many will always be found completely atrophied and converted into a mass of dense hyaline tissue, which contains a few stellate or spindle-shaped cells. In nearly all of them the most marked feature is a thickening of the capillary walls The thickened capillaries are homogeneous, refractive, and similar to the tissue forming the thickened intima of the small arteries. In places this thickening proceeds to complete obliteration of the vessel, so that in the glomerulus there are areas in which no capillaries are found, the space being filled by a dense tissue containing small, irregular, and brightly staining cells. The cells of the glomerulus are in the early stages increased in number, both the cells of the blood capillaries and the cells of the covering epithelium. In one case the increase in the epithelial cells was particularly well marked. In many cases there was a growth of connective tissue into the glomerulus which seemed to take place from the adventitia of the vessels of the root. The atrophy was brought about both by the occlusion of the vessels and by the advancing growth of the connective tissue. Coincident with these atrophic changes in the glomeruli and keeping pace with them there was a thickening of the capsule.

In the liver, in one of the best marked cases, there is some increase in the connective tissue in the portal spaces. The arteries show essentially the same conditions as those of the kidney—there is the same growth of tissue in the intima, and the same degeneration of the media. The liver-cells in general are much smaller than normal; they are often fatty, and a few completely necrotic cells were found. The spaces between the rows of liver-cells are broader than normal. The most striking change in the liver is the thickening of the capillary walls by a tissue very similar to that producing the thickening of the glomerular capillaries. To this tissue the marked resistance and toughness of the liver is due. It is homogeneously distributed all through the liver, but in some places is much more abundant and much denser than in others, and from these areas it seems to radiate out in all directions. The capillaries are but little reduced in diameter, all the thickening apparently taking place outside of the vessel between it and the rows of liver-cells. Sometimes processes from this tissue were given off

which penetrated between the cells. Another marked feature which was so often present in these livers as to almost constitute an integral part of the changes, was a fatty degeneration of the stellate cells. These peculiar cells, first described by Kupper, lying outside of the capillaries, between them and the liver-cells, give a remarkable appearance to the fresh sections. The section appears to be sprinkled with dark stellate figures. In one of the livers there were sharply circumscribed foci of necrosis, and in the capillaries between the rows of necrotic cells and outside of the capillaries between the cells themselves were immense numbers of leucocytes.

The histological changes in the aorta and the larger bloodvessels are very analogous to those which we have described as taking place in the smaller. They present such manifold variations that it would take us too long to enter into a complete description of them. The two essential changes are various degenerative changes in the media and a growth of tissue in the intima. The degenerations in the media are shown in various ways. Sections of the fresh artery show some fatty degeneration, but this does not play the chief part. The most common change seems to be necrosis and hyaline degeneration. The muscle-cells lose their nuclei and the whole muscular coat is changed into a solid homogeneous mass. Even the elastic fibres between the muscle laminæ are frequently broken up and disappear. In some sections of the dilated carotid, the media as such could not be recognized, the whole artery being changed into a dense, thick mass of sclerosed connective tissue. This atrophy of the media is always best marked opposite the points of greatest thickening of the intima. The tissue composing the thickened intima consists of thick layers of dense connective tissue, which not only in consequence of the poor nutrition which it has, but also in consequence of the pressure to which it is subjected, is particularly prone to degenerative changes. The tendency to degenerative changes, however, is not so marked here as it is in the senile form.

This diffuse arterio-sclerosis which we have described agrees best with the form which Thoma has described as secondary arterio-sclerosis, and in which he considers that the changes in the large arteries are due to the resistance to the blood circulation which the diseased small arteries causes. In a paper on the conditions of the vessels in Bright's disease, which preceded his publications on the arteries, he shows that there is an opposition to the passage of the

blood, which is due primarily not to a narrowing of the calibre of the vessels by the thickening of the intima, but by an increased permeability of the vessel walls. With this disease of the vessels there is an increase in the connective tissue and destruction of large numbers of capillaries, still further diminishing the size of the vascular bed, and then comes a disparity between the calibre of the artery and the territory to be supplied, followed by a compensating growth of connective tissue. This endarteritis of distant organs is extended in the same way to the aorta. We would rather take the view that the changes in the aorta and in the minute arteries are due to the same cause; that in the diffuse endarteritis we have a disease which is primarily due to a degeneration of the muscular fibres of the media. On this the growth of the intima follows, which is due to the same cause acting in two ways: in one, by the well-known law of connective-tissue growth, to supply a defect, in this case the degeneration of the media; and in the other, possibly acting under the law of Thoma, a compensating endarteritis to restore the abnormally dilated vessel to a normal calibre. Thoma's assumption that his secondary arterio-sclerosis is due to an increased blood pressure in the aorta from the increased peripheral resistance cannot be proven. On the contrary, we know that we may have heart atrophy with regurgitation at the aortic orifice, where the pressure in the aorta is certainly momentarily increased, without any affection of the intima. In this case we might suppose that the sudden pressure, followed by relaxation, would be fully as injurious to the media as continued pressure. We know further that we may have continuous increased pressure in the aorta from peripheral resistance without any degeneration of the media and without any arterio-sclerosis. Examples enough are furnished of this in various renal lesions with heart hypertrophy. It is probable that increased pressure alone will not affect the media, and the integrity of the vessel can be preserved.

There can be no doubt that this secondary compensating endarteritis of Thoma plays a most important part in pathology. We find it, as Thoma has shown, in an artery the area of whose bed of distribution has been diminished or destroyed, whether by a destruction of tissue, as in the case of an infarction, or in an amputation stump. In the cases of this, however, which we have seen, there was the great difference from the primary process, in that the media was intact in

most, and certainly in the most recent cases, the growth apparently taking place from the intima without any destruction of media. The change which finally takes place in the media is the slow atrophy of an unused tissue. Not only do we find this growth of the intima following degeneration of the media in the diffuse arterio-sclerosis, but we find it in the nodular endarteritis in whatever way produced. In a case of syphilitic endarteritis reported by Thomas, in which gummata were found in the walls of the vessels, there was a growth in the intima, always most intense opposite the affected wall.

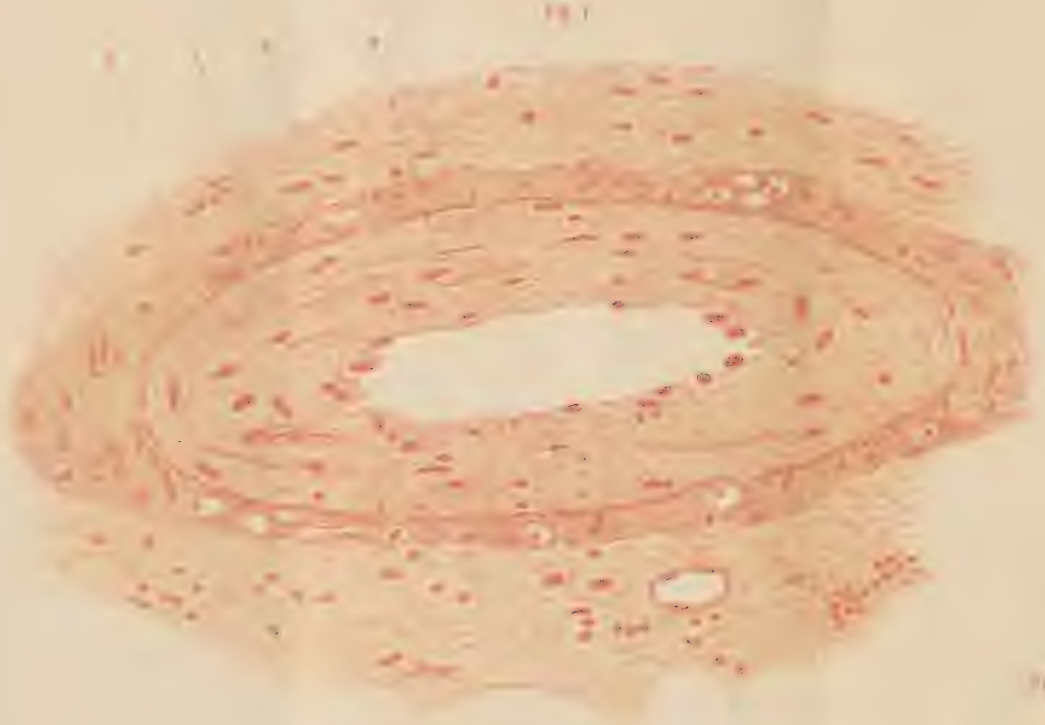
Are the changes in the kidney and liver the result of the arterial changes? We think they are. While in advanced atrophy of the organ, from whatever cause, we have some thickening of the vessels which is of the nature of Thoma's compensating endarteritis, they are not so prominent as they are in these cases, nor are they of the same nature. The changes in the arterioles and glomeruli of the kidney, and the arteries and capillaries of the liver, are too distinctive to suppose that they are secondary. We do not find similar changes in the bloodvessels of either organ when we have every reason to believe that the lesions are due to other causes. In cirrhosis of the liver there may be some thickening of the intima of the vessels of a compensatory character, but the lesions consist rather in thickening of the adventitia than the intima, and the lesions of the media are absent.

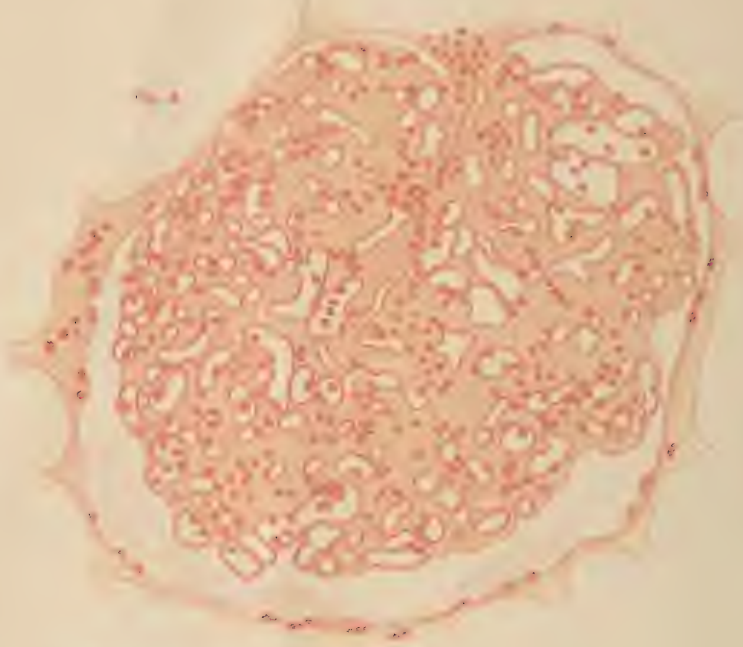
The affections of the kidneys are both general, and there are foci of more intense atrophy where there are large defects similar to those left by infarctions, and we find in the most advanced disease sometimes complete occlusion in the corresponding arteries. The nature of the atrophic lesions in the epithelium do not offer us any certain criterion to judge by. We may find fatty and hyaline degeneration of the epithelial cells in a variety of conditions, but we are not so apt to find simple atrophy, diminution in size of cells, so marked in other conditions. The increase in the connective tissue also is not distinctive. It follows atrophy here, as in all other places. That it does follow and not precede atrophy can be seen best on a close study of the glomeruli; we find thickening of the capsule and growth of the surrounding connective tissue, and atrophic changes in the vascular tuft at the same time. We find the earlier stages of these changes in the capillaries without any change in the capsule,

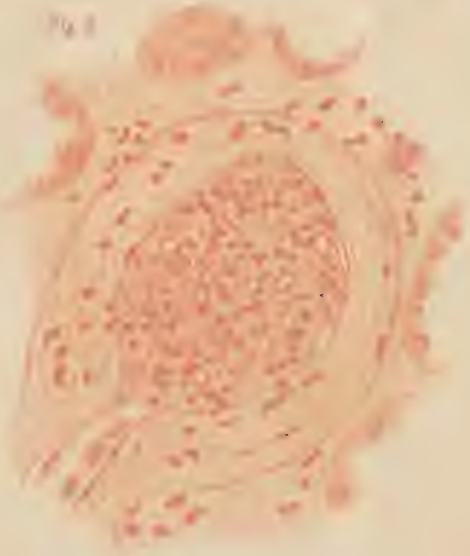
but we do not find the thickening of the capsule without any changes in the tuft. The nutrition of the kidney is probably more interfered with by the disease of the glomeruli than in any other way; for it must be remembered that all the renal blood, with the exception of that provided for by the few anastomoses, passes through the glomeruli. The closure of the capillaries is in part compensated for by anastomoses of the glomerular vessels with the vessels of the capsule, and by dilatation and closer anastomoses of some of the loops.

It would be difficult to conceive of any series of pathological conditions so closely bound together, and in which every lesion so tends to intensify some preceding lesions, as we have given us in this disease. First, the arterial changes, producing not only resistance to blood circulation with increased pressure and heart atrophy, but changes in the tissue of the kidney, interference with its proper functions, and the still further increase of blood pressure and heart hypertrophy in consequence of this. We must add to this the effect on the circulation of an overloaded venous system, due to the chronic passive congestion which is almost sure to come on sooner or later when the valves are incompetent for the dilated heart.

We think that these lesions which we have described should be clearly separated from the senile endarteritis and the lesions accompanying this. The senile endarteritis is a disease of advanced life, seldom occurring before the age of fifty. The lesions in the vessels are slow, and there is little reaction to the degeneration. While the tissue-changes are probably in part dependent on the arterial lesions, the close connection cannot be traced. Clinically, there is absence of the high arterial pressure which constitutes the most obvious clinical manifestation of the diffuse arterio-sclerosis. The diffuse arterio-sclerosis is a definite disease; the lesions in the arteries and tissues form a pathological entity, and the primary lesion to which all the changes are due is a degeneration of the tissue of the media of both the large and smaller arteries.







Description of Plate.

Fig. I.—Oblique section of a small artery in the kidney. *a*, thickened intima; *b*, elastic coat; *c*, muscular coat; *d*, surrounding connective tissue. The most marked change is seen in the thickening of the intima and the degeneration of the muscular coat. The elastic lamella is broken in places and the folds are lost.

Fig. II.—The two smallest of these arteries are from the liver; the larger from the kidney. In the smallest arteries the lumen is very narrow and irregular. The intima is very much thickened, and the muscular coat can hardly be recognized as such. In the upper figure the elastic lamella has disappeared in one portion of the vessel.

Fig. III.—Glomerulus in an advanced stage of atrophy. The vessels are almost entirely obliterated, the whole is greatly shrunken, and the wall of the capsule is thickened.

Fig. IV.—A glomerulus in an early stage of atrophy. The walls of the capillaries are thickened. The lumen of many of them is very small and irregular, and there is considerable connective tissue growing between them. In places this connective tissue is rich in cells. There is little or no shrinkage of the glomerulus, and no thickening of the capsule. The granular material in the space between the glomerulus and the capsule is coagulated albumin.

(Figs. I., II., III., IV. are all drawn with camera lucida. Zeiss obj. d.ocl. 2.)

Fig. V.—Small portion of the muscular coat of a larger artery, more highly magnified. The spaces in this mark the degenerated muscular fibres. Between these is connective tissue very similar to that forming the thickened intima.